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(54) **Succinimide derivates and process for preparation thereof.**

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US-A-3 184 456

CHEMICAL ABSTRACTS, vol. 81, no. 1, 8th July 1974, page 317, no. 3882x, Columbus, Ohio, USA R.N. ZAGIDULLIN: "Cyanoethylation of N-(beta-aminoethyl)piperazine and its derivatives"

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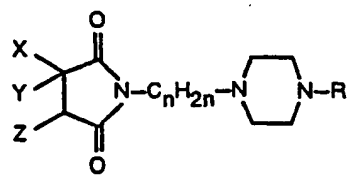
Description

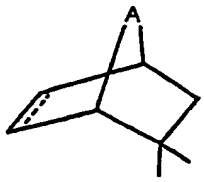
This invention relates to n vel succinimide derivatives. More particularly, it relates to novel succinimide derivatives substituted with piperazinylalkyl group at the imido-nitrogen atom, which have antianxious activity, and process for preparation thereof and pharmaceutical composition comprising the same for treatment of anxiety state. In US—A—3,184,456, US—A—2,928,846 and FR—A—2,506,771 structurally similar imides having different effects are disclosed.

The succinimide derivatives of this invention are represented by the following formula:

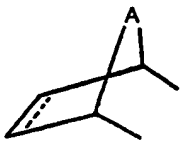


(I)

wherein X and Y are combined to form a group of the formula:



(wherein A is an oxygen atom, a methylene group or an ethylene group and a full line accompanying a broken line (------) is a single bond or a double bond) and Z is a hydrogen atom or, X and Z are combined to form a group of the formula:

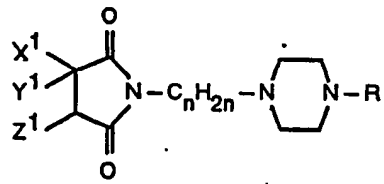


(wherein A and a full line accompanying a broken line are each as defined above) and Y is a hydrogen atom, R is a phenyl group, optionally substituted with halogen, C_1—C_4 alkyl, C_1—C_4 alkoxy or trifluoromethyl, a 2-pyridyl group or a 2-pyrimidinyl group and n is an integer of 3 or 4, and pharmaceutically acceptable acid addition salts thereof.

The term and definitions used in this specification are illustrated as follows:

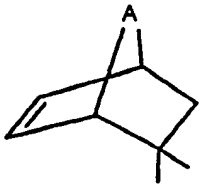
Partial structure  is intended to mean both of  .

Accordingly, it is to be understood that the formula (I) includes two series of compounds, one of which is represented by the formula:

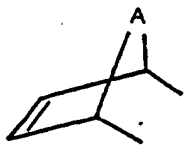


(Ia)

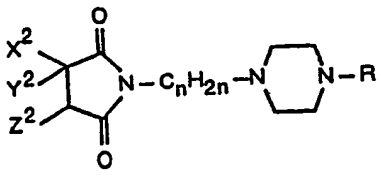
wherein X^1 and Y^1 are combined to form a group of the formula:



(wher in A is as defined above) and Z^1 is a hydrogen atom or, X^1 and Z^1 are combined to form a group of the formula:

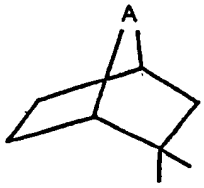


(wherein A is as defined above) and Y^1 is a hydrogen atom, and R and n are each as defined above, and the other is represented by the formula:



(Ib)

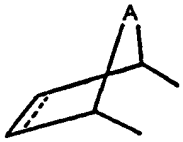
wherein X^2 and Y^2 are combined to form a group of the formula:



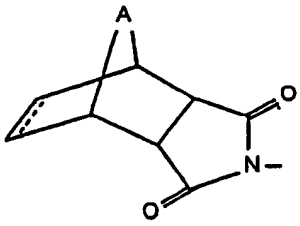
(wherein A is as defined above) and Z^2 is a hydrogen atom, or X^2 and Z^2 are combined to form a group of the formula:

(wherein A is as defined above) and Y^2 is a hydrogen atom, and R and n are each as defined above.

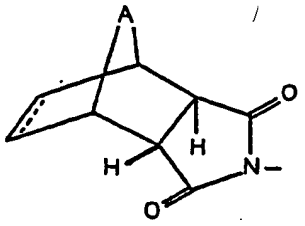
When X and Z are combined to form a group of the formula:



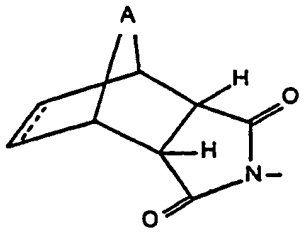
the succinimide derivative (I) has partial structure of the following formula:



which is intended t mean both of the ge m tric f rmulae:



and



(a) (b)

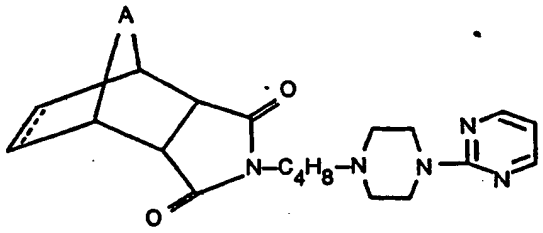
wherein A is as defined above.

When A and

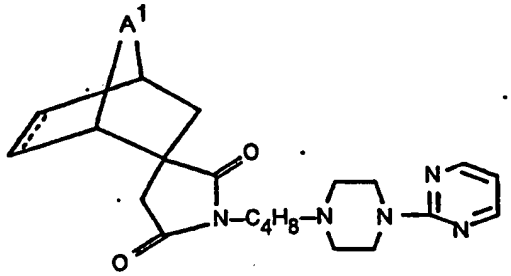
are different (i.e. not ethylene simultaneously), the formulae (a) and (b) represent different partial structures. The formula (a) represents a partial structure in which A and the imido group are located on the same side in respect of the six-membered carbocycle, and is referred to as "exo". The formula (b) represents a partial structure in which A and the imido group are located on the different side in respect of the six-membered carbocycle, and is referred to as "endo". It is to be understood that the compound (I) includes both of the "exo" isomer and "endo" isomer, and the mixture of them.

The term "halogen" may include chlorine, bromine, iodine and fluorine. The term "C_1—C_4 alkyl" may include a residue of straight or branched alkane having 1 to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl and isobutyl. The term "C_1—C_4 alkoxy" may include a residue in which straight or branched alkane having 1 to 4 carbon atoms is bonded with a bivalent oxygen such as methoxy, ethoxy, propoxy, isopropoxy and butoxy. The group "—C_nH_{2n}—" may include a residue of straight or branched alkylene having 3 or 4 carbon atoms such as trimethylene, methyltrimethylene and tetramethylene.

Preferable compounds in the succinimide derivatives (I) are those represented by the formulae:



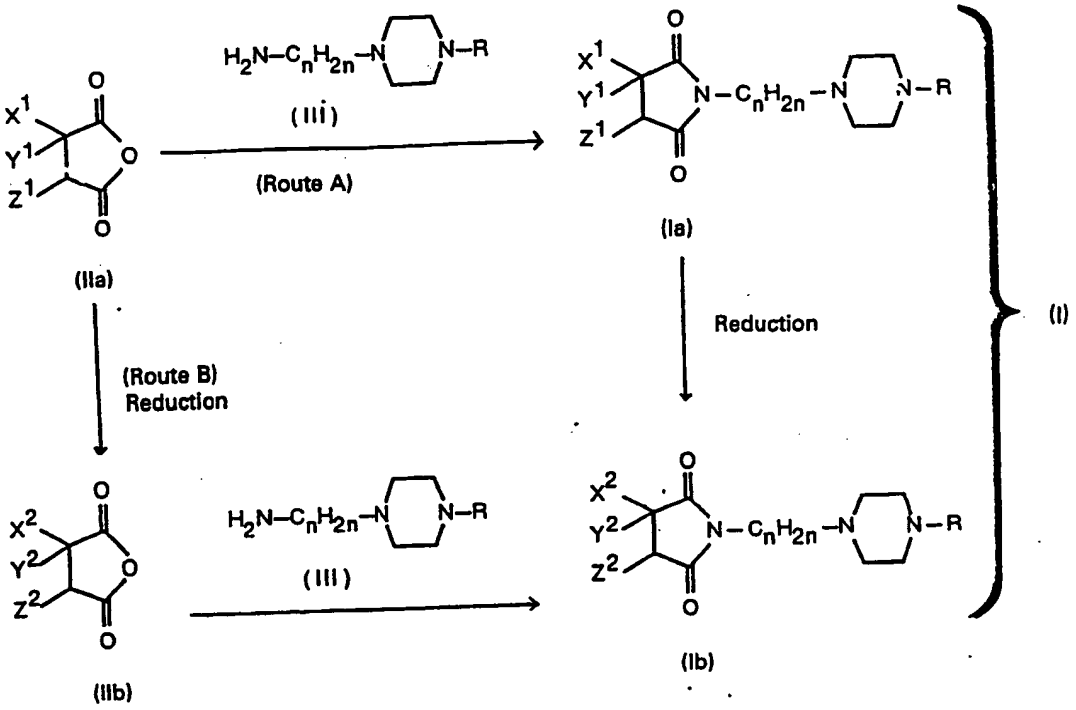
and



wherein A^1 is a methylene group or an ethylene group.

Suitable pharmaceutically acceptable acid addition salts are conventional non-toxic salts and may be a salt with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, etc. or a salt with an organic acid such as acetic acid, propionic acid, butyric acid, tartaric acid, citric acid, maleic acid, fumaric acid, etc.

The succinimide derivatives of this invention can be prepared by processes as shown in the following scheme:



wherein X^1, X^2, Y^1, Y^2, Z^1, Z^2, n and R are each as defined above.

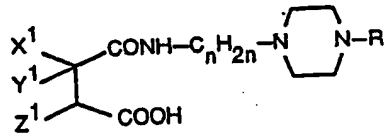
Said processes are explained in details in the following:

Route A

The compound (Ia) can be prepared by reacting the compound (IIa) with the amine (III). The starting compound (IIa) can be prepared by a process reported by T. V. Auken et al. (J. Org. Chem., *23*, 626 (1958)) or Inokuma et al. (Japanese Patent Publn. (unexamined) No. 145650/1979).

The reaction is usually carried out by heating the compound (IIa) and the amine (III) in a conventional inert solvent. Suitable solvents may include pyridine and n-butanol.

The reaction includes in its scope the cases that a half-amide compound of the formula:



(IVa)

wherein X^1, Y^1, Z^1, R and n are each as defined above is formed. The compound (IVa) takes in some cases a long period of time for cyclization to the compound (Ia). In such case, the cyclization may be easily effected by heating the compound (IVa) in an acetic anhydride. The obtained compound (Ia) may optionally be reduced to the compound (Ib).

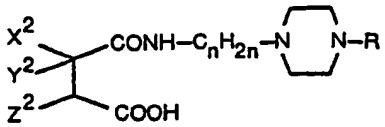
The reduction is usually carried out by hydrogenating the compound (Ia) in the presence of a hydrogenation catalyst in a solvent. Suitable hydrogenation catalysts may include conventional ones such as platinum catalysts (e.g. platinum black, platinum dioxide, platinum colloid), palladium catalysts (e.g. palladium black, palladium on carbon, palladium colloid), a rhodium catalyst and nickel catalysts (e.g. Raney nickel, nickel oxide). Suitable solvents ickel oxide). Suitable solvents may include lower alkanol (e.g. methanol, ethanol, isopropanol, water, acetic acid, ethyl acetate, tetrahydrofuran and dioxane. The hydrogenation may be carried out under either atmospheric pressure or increased pressure and at eith r ordinary temperature or elevated temperature.

Route B

The compound (Ib) can be prepared by reducing the compound (IIa) and then reacting the resultant compound (IIb) with the amine (III).

The reduction of the compound (IIa) to the compound (IIb) and the reaction of the compound (IIb) with the amin (III) may be conducted in a manner similar t that f the reduction f the compound (Ia) to the compound (Ib) and the reaction of the compound (IIa) with the amine (III), resp ctively.

The reaction of the compound (IIb) with the amine (III) to produce the compound (Ib) includes in its scope the cases that a half-amide compound of the formula:



(IVb)

wherein X^2, Y^2, Z^2, R and n are each as defined above is formed as an intermediate, and the compound (IVb) may be imidated to the compound (Ib) in a manner similar to that of the compound (IVa).

Some examples of the compound of the formula (I) are listed below:

N-[4-{4-(2-Pyrimidinyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2,3-di-exo-carboximide;
N-[4-{4-(2-Pyridyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2,3-di-exo-carboximide;
N-[4-{4-(2-Chlorophenyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2,3-di-exo-carboximide;
N-[4-{4-(2-Trifluoromethylphenyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2,3-di-exo-carboximide;
N-[4-{4-(2-Methylphenyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2,3-di-exo-carboximide;
N-[4-{4-(2-Methoxyphenyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2,3-di-exo-carboximide;
N-[3-{4-(2-Pyrimidinyl)-1-piperazinyl}propyl]bicyclo[2.2.1]heptane-2,3-di-exo-carboximide;
N-[3-{4-(2-Pyridyl)-1-piperazinyl}propyl]bicyclo[2.2.1]heptane-2,3-di-exo-carboximide;
N-[3-(4-Phenyl-1-piperazinyl)propyl]bicyclo[2.2.1]heptane-2,3-di-exo-carboximide;
N-[3-{4-(2-Chlorophenyl)-1-piperazinyl}propyl]bicyclo[2.2.1]heptane-2,3-di-exo-carboximide;
N-[4-{4-(2-Pyrimidinyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2,3-di-endo-carboximide;
N-[4-{4-(2-Pyridyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2,3-di-endo-carboximide;
N-[3-{4-(2-Pyrimidinyl)-1-piperazinyl}propyl]bicyclo[2.2.1]heptane-2,3-di-endo-carboximide;
N-[4-{4-(2-Pyrimidinyl)-1-piperazinyl}butyl]bicyclo[2.2.2]octane-2,3-dicarboximide;
N-[4-{4-(2-Pyridyl)-1-piperazinyl}butyl]bicyclo[2.2.2]octane-2,3-dicarboximide;
N-[4-{4-(2-Pyrimidinyl)-1-piperazinyl}butyl]-7-oxabicyclo[2.2.1]heptane-2,3-di-exo-carboximide;
N-[4-{4-(2-Pyridyl)-1-piperazinyl}butyl]-7-oxabicyclo[2.2.1]heptane-2,3-di-exo-carboximide;
N-[4-{4-(2-Pyrimidinyl)-1-piperazinyl}butyl]bicyclo[2.2.1]hept-5-ene-2,3-di-exo-carboximide;
N-[4-{4-(2-Pyridyl)-1-piperazinyl}butyl]bicyclo[2.2.1]hept-5-ene-2,3-di-exo-carboximide;
N-[4-{4-(2-Pyrimidinyl)-1-piperazinyl}butyl]bicyclo[2.2.1]hept-5-ene-2,3-di-endo-carboximide;
N-[4-{4-(2-Pyridyl)-1-piperazinyl}butyl]bicyclo[2.2.1]hept-5-ene-2,3-di-endo-carboximide;
N-[4-{4-(2-Pyrimidinyl)-1-piperazinyl}butyl]bicyclo[2.2.1]oct-5-ene-2,3-di-endo-carboximide;
N-[4-{4-(2-Pyridyl)-1-piperazinyl}butyl]bicyclo[2.2.1]oct-5-ene-2,3-di-endo-carboximide;
N-[4-{4-(2-Pyrimidinyl)-1-piperazinyl}butyl]-7-oxabicyclo[2.2.1]hept-5-ene-2,3-di-exo-carboximide;
N-[4-{4-(2-Pyridyl)-1-piperazinyl}butyl]-7-oxabicyclo[2.2.1]hept-5-ene-2,3-di-exo-carboximide;
N-[4-{4-(3-Chlorophenyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2,3-di-exo-carboximide;
N-[4-{4-(4-Chlorophenyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2,3-di-exo-carboximide;
N-[4-{4-(2-Pyrimidinyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2-exo-2-endo-methylene-dicarboximide;
N-[4-{4-(2-Pyridyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2-exo-2-endo-methylenedicarboximide;
N-[4-{4-(2-Chlorophenyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2-exo-2-endo-methylene-dicarboximide;
N-[4-{(4-(2-Trifluoromethylphenyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2-exo-2-endo-methylenedicarboximide;
N-[4-{4-(2-Methylphenyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2-exo-2-endo-methylene-dicarboximide;
N-[4-{4-(2-Methoxyphenyl)-1-piperazinyl}butyl]bicyclo[2.2.1]heptane-2-exo-2-endo-methylene-dicarboximide;
N-[4-(4-Phenylpiperazinyl)butyl]bicyclo[2.2.1]heptane-2-exo-2-endo-methylenedicarboximide;
N-[4-{4-(2-Pyrimidinyl)-1-piperazinyl}butyl]bicyclo[2.2.1]hept-5-ene-2-exo-2-endo-methylene-dicarboximide;
N-[4-{4-(2-Pyridyl)-1-piperazinyl}butyl]bicyclo[2.2.1]hept-5-ene-2-exo-2-endo-methylene-dicarboximide;
N-[4-{4-(2-Chlorophenyl)-1-piperazinyl}butyl]bicyclo[2.2.1]hept-5-ene-2-exo-2-endo-methylene-dicarboximide;
N-[4-{4-(2-Methylphenyl)-1-piperazinyl}butyl]bicyclo[2.2.1]hept-5-ene-2-exo-2-endo-methylene-dicarboximide;
N-[4-{4-(2-Methoxyphenyl)-1-piperazinyl}butyl]bicyclo[2.2.1]hept-5-ene-2-exo-2-endo-methylene-dicarboximide;
N-[4-(4-Phenylpiperazinyl)butyl]bicycl [2.2.1]hept-5-ene-2-exo-2-endo-methyl nedicarboximide;
N-[3-{4-(2-Pyrimidinyl)-1-piperazinyl}propyl]bicycl [2.2.1]heptane-2-exo-2-endo-methylene-dicarboximide;
N-[3-{4-(2-Pyridyl)-1-piperazinyl}propyl]bicyclo[2.2.1]heptane-2-exo-2-endo-methylenedicarboximide;

N-[3-{4-(2-Chlorophenyl)-1-piperazinyl}propyl]bicyclo[2.2.1]heptane-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Methylphenyl)-1-piperazinyl}propyl]bicyclo[2.2.1]heptane-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Methoxyphenyl)-1-piperazinyl}propyl]bicyclo[2.2.1]heptane-2-exo-2-endo-methylenedicarboximide;
N-[3-[4-Phenylpiperazinyl)propyl]bicyclo[2.2.1]heptane-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Pyrimidinyl)-1-piperazinyl}propyl]bicyclo[2.2.1]hept-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Pyridyl)-1-piperazinyl}propyl]bicyclo[2.2.1]hept-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Chlorophenyl)-1-piperazinyl}propyl]bicyclo[2.2.1]hept-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Methylphenyl)-1-piperazinyl}propyl]bicyclo[2.2.1]hept-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Methoxyphenyl)-1-piperazinyl}propyl]bicyclo[2.2.1]hept-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[3-(4-Phenylpiperazinyl)propyl]bicyclo[2.2.1]hept-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[4-{4-(2-Pyrimidinyl)-1-piperazinyl}butyl]bicyclo[2.2.2]octane-2-exo-2-endo-methylenedicarboximide;
N-[4-{4-(2-Pyridyl)-1-piperazinyl}butyl]bicyclo[2.2.2]octane-2-exo-2-endo-methylenedicarboximide;
N-[4-{4-(2-Chlorophenyl)-1-piperazinyl}butyl]bicyclo[2.2.2]octane-2-exo-2-endo-methylenedicarboximide;
N-[4-{4-(2-Trifluoromethylphenyl)-1-piperazinyl}butyl]bicyclo[2.2.2]octane-2-exo-2-endo-methylenedicarboximide;
N-[4-{4-(2-Methylphenyl)-1-piperazinyl}butyl]bicyclo[2.2.2]octane-2-exo-2-endo-methylenedicarboximide;
N-[4-{4-(2-Methoxyphenyl)-1-piperazinyl}butyl]bicyclo[2.2.2]octane-2-exo-2-endo-methylenedicarboximide;
N-[4-(4-Phenylpiperazinyl)butyl]bicyclo[2.2.2]octane-2-exo-2-endo-methylenedicarboximide;
N-[4-{4-(2-Pyrimidinyl)-1-piperazinyl}butyl]bicyclo[2.2.2]oct-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[4-{4-(2-Pyridyl)-1-piperazinyl}butyl]bicyclo[2.2.2]oct-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[4-{4-(2-Chlorophenyl)-1-piperazinyl}butyl]bicyclo[2.2.2]oct-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[4-{4-(2-Methylphenyl)-1-piperazinyl}butyl]bicyclo[2.2.2]oct-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[4-{4-(2-Methoxyphenyl)-1-piperazinyl}butyl]bicyclo[2.2.2]oct-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[4-(4-Phenylpiperazinyl)butyl]bicyclo[2.2.2]oct-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Pyrimidinyl)-1-piperazinyl}propyl]bicyclo[2.2.2]octane-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Pyridyl)-1-piperazinyl}propyl]bicyclo[2.2.2]octane-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Chlorophenyl)-1-piperazinyl}propyl]bicyclo[2.2.2]octane-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Methylphenyl)-1-piperazinyl}propyl]bicyclo[2.2.2]octane-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Methoxyphenyl)-1-piperazinyl}propyl]bicyclo[2.2.2]octane-2-exo-2-endo-methylenedicarboximide;
N-[3-(4-Phenylpiperazinyl)propyl]bicyclo[2.2.2]octane-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Pyrimidinyl)-1-piperazinyl}propyl]bicyclo[2.2.2]oct-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Pyridyl)-1-piperazinyl}propyl]bicyclo[2.2.2]oct-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Chlorophenyl)-1-piperazinyl}propyl]bicyclo[2.2.2]oct-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Methylphenyl)-1-piperazinyl}propyl]bicyclo[2.2.2]oct-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[3-{4-(2-Methoxyphenyl)-1-piperazinyl}propyl]bicyclo[2.2.2]oct-5-ene-2-exo-2-endo-methylenedicarboximide;
N-[3-(4-Phenylpiperazinyl)propyl]bicyclo[2.2.2]oct-5-ene-2-exo-2-endo-methylenedicarboximide; etc.

The antianxious activity of the succinimide derivatives according to the invention could be proved by anti-conflict test. The anti-conflict test was carried out according to the process of Geller and Sifter [Psychopharmacologia, *1*, 482 (1960)].

Hungry male rats (Kitayama) of Wistar strain which were previously trained to take feed by lever

were negatively reinforced by r ceiving an electric shock on levering. As a result, th rats fell into conflict and stopped l vering. When antianxiety substance was administ red to the rats, the rats restarted levering despite receiving the electric shock. Frequ ncy of the levering under the electric shock was used for indicati n of anti-conflict activity r antianxious activity of test substance. The test substances were administered intraperitoneally to the rats. Test were carried out while the activity of the substances were the maximum. The known antianxiety drug "Diazepam" was used for the control. Each dose of 2 mg/kg (i.p.) of N - [4 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}butyl]bicyclo[2.2.1]heptane - 2 - exo - 2 - endo - methylenedicarboximide hydrochloride (Compound A), N - [4 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}-butyl]bicyclo[2.2.2]octane - 2 - exo - 2 - endo - methylenedicarboximide hydrochloride (Compound B) or N - [4 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}butyl]bicyclo[2.2.1]heptane - 2,3 - di - exo - carboximide hydrochloride (Compound C) had an approximately equal anti-conflict activity or antianxiety activity to 1 mg/kg (i.p.) of Diazepam, and afforded no substantial influence on the general behavior.

Further, none of the compounds (A), (B) and (C) showed any significant effect at a dose of 100 mg/kg (per os) on hexobarbital anesthesia which is an indication of depressing side effects such as sleepiness, while Diazepam reinforced the anesthesia significantly. It was proved from these results that the compounds (A), (B) and (C) are selective antianxiety drugs with less central nervous side effects.

For therapeutic administration, the compound (I) or the salt thereof is used in the form of conventional pharmaceutical preparations suitable for oral administration, for example, tablet, capsule, syrup, suspension, etc., or those suitable for parenteral administration, for example, solution, emulsion, suspension, etc. for injection, or suppository for rectal administration. If needed, there may be included in the above preparations buffers, solubilizer, isotonizers, etc.

While the dosage of the compound (I) may vary from and also depend upon the degree of the infection, age and weight of patient and dosage forms, the active compound can be, in general, administered to an adult in an amount between 1 mg and 300 mg, preferably 5 mg and 100 mg per day in single dose or divided doses.

The invention will now be further illustrated by means of the following Examples, which are not, however, intended to limit the scope of the invention.

Example 1

A mixture of norbornane - 2,3 - di - endo - carboxylic anhydride (500 mg, 3 mmol), 1 - (4 - aminobutyl) - 4 - (2 - pyrimidinyl)piperazine (708 mg, 3 mmol) and pyridine (12.1 ml) was refluxed for 5 hours. The solvent was removed from the mixture under reduced pressure. The residue was purified by silica gel chromatography using chloroform as an eluent. The oily substance obtained was treated with 6% hydrogen chloride/isopropanol. The solvent was removed and the residue was recrystallized from isopropanol to give N - [4 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}butyl]bicyclo[2.2.1]heptane - 2,3 - di - endo - carboximide hydrochloride (920 mg, 67.2%). M.P., 202—203°C.

Example 2

A mixture of norbornane - 2,3 - di - exo - carboxylic anhydride (636 mg, 3.8 mmol), 1 - (4 - aminobutyl) - 4 - (2 - pyrimidinyl)piperazine (900 mg, 3.8 mmol) and pyridine (15.4 ml) was refluxed for 11 hours. Then the mixture was post-treated in a manner similar to that in Example 1 to give N - [4 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}butyl]bicyclo[2.2.1]heptane - 2,3 - di - exo - carboximide hydrochloride (from isopropanol). M.P., 227—229°C.

Example 3

A mixture of bicyclo[2.2.2]octane - 2,3 - dicarboxylic anhydride (541 mg, 3 mmol), 1 - (4 - aminobutyl) - 4 - (2 - pyrimidinyl)piperazine (708 mg, 3 mmol) and pyridine (12.1 ml) was refluxed for 10 hours. The solvent was removed from the mixture under reduced pressure. The residue was extracted with chloroform and water. The chloroform layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude crystals (1 g), which were treated with 6% hydrogen chloride/ isopropanol. The solvent was removed to give N - [4 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}butyl]-bicyclo[2.2.2]octane - 2,3 - dicarboxamide hydrochloride (from ethanol). M.P., 198—200°C.

Example 4

A mixture of 7 - oxabicyclo[2.2.1]heptane - 2,3 - di - exo - carboxylic anhydride (1 g, 5.95 mmol), 1 - (4 - aminobutyl) - 4 - (2 - pyrimidinyl)piperazine (1.4 g, 5.95 mmol) and pyridine (23.9 ml) was refluxed for 12 hours. Then, the mixture was post-treated in a manner similar to that in Example 1 to give N - [4 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}butyl] - 7 - oxabicyclo[2.2.1]heptane - 2,3 - di - exo - carboximide hydrochloride (from isopropanol). M.P., 210—213°C.

Example 5

A mixture of bicyclo[2.2.1]hept - 5 - ene - 2,3 - di - exo - carb xylic anhydride (2.2 g, 13.56 mmol), 1 - (3 - aminopropyl) - 4 - (2 - pyrimidinyl)piperazine (3 g, 13.56 mm l) and pyridine (53 ml) was refluxed for 7 hours. The solv nt was removed from the mixture under reduc d pressure. The residue was dissolved in chloroform and filtered thr ugh a pad of silica gel. The filtrate was concentrated under reduced pr ssure

t giv crystals (3.91 g, 78%), which were treated with 5% hydrogen chloride/isopropan l. The solvent was rem v d and the residu was r crystallized from isopr panol to give N - [3 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}pr pyl]bicycl [2.2.1]hept - 5 - ene - 2,3 - di - exo - carboximide hydrochloride. M.P., 209—212°C.

Example 6

A mixture of N - [3 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}propyl]bicyclo[2.2.1]hept - 5 - ene - 2,3 - di - exo - carboximide (2.7 g, 7.35 mmol), 5% palladium on carbon (270 mg) and tetrahydrofuran (27 ml) was hydrogenated for 2 hours. The mixture was filtered and the filtrate was concentrated under reduced pressure to give crude crystals, which were treated with 5% hydrogen chloride/isopropanol. The solvent was removed and the residue was recrystallized from ethanol/isopropanol to give N - [3 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}propyl]bicyclo[2.2.1]heptane - 2,3 - di - exo - carboximide hydrochloride. M.P. 216—217°C.

Example 7

A mixture of bicyclo[2.2.1]hept - 5 - ene - 2,3 - di - exo - carboxylic anhydride (2.4 g, 14.5 mmol), 1 - (3 - aminopropyl) - 4 - (2 - pyridyl)piperazine (3.2 g, 14.5 mmol) and pyridine (58.2 ml) was refluxed for 6 hours. The solvent was removed from the mixture under reduced pressure. Acetic anhydride (58.2 ml) was added to the residue and the mixture was refluxed for 30 minutes. Again, the solvent was removed fr m the mixture and the residue was purified by silica gel chromatography using chloroform as an eluent. The oily substance obtained was treated with 15% hydrogen chloride/isopropanol. The solvent was removed and the residue was recrystallized to give N - [3 - {4 - (2 - pyridyl) - 1 - piperazinyl}propyl]bicyclo[2.2.1]-hept - 5 - ene - 2,3 - di - exo - carboximide hydrochloride. M.P., 248—250°C.

Example 8

A mixture of N - [3 - {4 - (2 - pyridyl) - 1 - piperazinyl}propyl]bicyclo[2.2.1]hept - 5 - ene - 2,3 - di - exo - carboximide hydrochloride (3.8 g, 10.3 mmol), 5% palladium on carbon (380 mg) and methanol (38 ml) was hydrogenated for 6 hours. Then, the mixture was treated in a manner similar to that in Example 6 to give N - [3 - {4 - (2 - pyridyl) - 1 - piperazinyl}propyl]bicyclo[2.2.1]heptane - 2,3 - di - exo - carboximide hydrochloride (from isopropanol). M.P., 254—256°C.

Example 9

A mixture of bicyclo[2.2.1]hept - 5 - ene - 2,3 - bi - exo - carboxylic anhydride (1.5 g, 9.03 mmol), 1 - (3 - aminopropyl) - 4 - phenylpiperazine (2 g, 9.03 mmol) and pyridine (36 ml) was refluxed for 7 hours. The solvent was removed from the mixture to give crude crystals (3.6 g). The crude crystals were dissolv d in chloroform and treated with activated carbon (72 mg) and silica gel (7.1 g) at room temperature for 1 hour. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was treated with 15% hydrogen chloride/isopropanol. The solvent was removed to give N - [3 - (4 - phenyl - 1 - piperazinyl)propyl]bicyclo[2.2.1]heptane - 2,3 - di - exo - carboximide hydrochloride. M.P., 245—248°C.

Example 10

A mixture of bicyclo[2.2.1]hept - 5 - ene - 2,3 - di - exo - carboxylic anhydride (1.9 g, 11.8 mmol), 1 - (3 - aminopropyl) - 4 - (2 - chlorophenyl)piperazine (3 g, 11.8 mmol) and pyridine (47.4 ml) was refluxed for 7 hours. Then, the mixture was post-treated in a manner similar to that in Example 9 to give N - [3 - {4 - (2 - chlorophenyl) - 1 - piperazinyl}propyl]bicyclo[2.2.1]hept - 5 - ene - 2,3 - di - exo - carboximide hydrochloride. M.P., 204—206°C.

Example 11

A mixture of N - [3 - {4 - (2 - chlorophenyl) - 1 - piperazinyl}propyl]bicyclo[2.2.1]hept - 5 - ene - 2,3 - di - exo - carboximide (2 g, 5 mmol), 5% palladium or carbon (200 g) and tetrahydrofuran (20 ml) was hydrogenated for 6 hours. Then, the mixture was post-treated in a manner similar to that in Example 6 to give N - [3 - {4 - (2 - chlorophenyl) - 1 - piperazinyl}propyl]bicyclo[2.2.1]heptane - 2,3 - di - exo - carboximide hydrochloride. M.P., 207—209°C.

Example 12

A mixture of bicyclo[2.2.1]hept - 5 - ene - 2,3 - di - endo - carboxylic anhydride (1.76 g, 11 mmol), 1 - (3 - aminopropyl) - 4 - (2 - pyrimidinyl)piperazine (2.37 g, 11 mmol) and pyridine (43 ml) was refluxed for 13 hours. Then, the mixture was post-treated in a manner similar to that in Example 1 to give N - [3 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}propyl]bicyclo[2.2.1]hept - 5 - ene - 2,3 - di - endo - carboximide hydrochloride (from isopr panol). M.P., 244—245°C.

Example 13

A mixture of N - [3 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}propyl]bicyclo[2.2.1]h pt - 5 - ene - 2,3 - di - ndo - carb ximid (3.4 g, 9.25 mm l), 5% palladium on carbon (340 mg) and tetrahydrofuran (34 ml)

was hydr genat d for 3 hours. Th , the mixture was post-treated in a mann r similar t that in Example 6 to give N - [3 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}pr pyl]bicycl [2.2.1]heptane - 2,3 - di - nd - carboximide hydrochl rid (from is propanol). M.P., 228—230°C.

Example 14

A mixture of bicyclo[2.2.1]heptane - 2 - exo - 2 - endo - methylenedicarboxylic anhydride (765 mg, 4,25 mmol), 1 - (4 - aminobutyl) - 4 - (2 - pyrimidinyl)piperazine (1 g, 4.25 mmol) and pyridine (17.1 ml) was refluxed for 6 hours. Then, the solvent was removed from the mixture under reduced pressure and the residue was purified by silica gel chromatography using chloroform as an eluent. The oily substance obtained was treated with 15% hydrogen chloride/isopropanol to give N - [4 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}butyl]bicyclo[2.2.1]heptane - 2 - exo - 2 - endo - methylenedicarboximide hydrochloride. M.P., 230—235°C.

Example 15

A mixture of bicyclo[2.2.1]heptane - 2 - exo - 2 - endo - methylenedicarboxylic anhydride (1.63 g, 9.04 mmol), 1 - (3 - aminopropyl) - 4 - (2 - pyrimidinyl)piperazine (2 g, 9.04 mmol) and n-butanol (20 ml) was refluxed for 9 3/4 hours. Then, the mixture was post-treated in the similar manner as that in Example 14 except that 5% hydrogen chloride was used in place of 15% hydrogen chloride to give N - [3 - {4 - (2 - pyrimidinyl - 1 - piperazinyl)propyl]bicyclo[2.2.1]heptane - 2 - exo - 2 - endo - methylenedicarboximide hydrochloride (from isopropanol) (1.9 g, 46.3%). M.P., 199—202°C.

Example 16

A mixture of bicyclo[2.2.1]heptane - 2 - exo - 2 - endo - methylenedicarboxylic anhydride (1.64 g, 9.09 mmol), 1 - (3 - aminopropyl) - 4 - (2 - pyridyl)piperazine (2 g, 9.08 mmol) and n-butanol (20 ml) was refluxed for 6 hours. Then, the mixture was post-treated in the similar manner as that in Example 14 except that 5% hydrogen chloride was used in place of 15% hydrogen chloride to give N - [3 - {4 - (2 - pyridyl) - 1 - piperazinyl}propyl]bicyclo[2.2.1]heptane - 2 - exo - 2 - endo - methylenedicarboximide hydrochloride (from ethanol/isopropanol) (2.9 g, 70.7%). M.P., 235—239°C.

Example 17

A mixture of bicyclo[2.2.1]heptane - 2 - exo - 2 - endo - methylenedicarboxylic anhydride (1.64 g, 9.08 mmol), 1 - (3 - aminopropyl) - 4 - phenylpiperazine (2 g, 9.08 mmol) and n-butanol (20 ml) was refluxed for 8 1/6 hours. Then, the mixture was post-treated in the similar manner as that in Example 14 except that 5% hydrogen chloride was used in place of 15% hydrogen chloride to give N - [3 - (4 - phenyl-piperazinyl)propyl]bicyclo[2.2.1]heptane - 2 - exo - 2 - endo - methylenedicarboximide hydrochloride (from isopropanol) (2.1 g, 51.2%). M.P., 229—234°C.

Example 18

A mixture of bicyclo[2.2.1]heptane - 2 - exo - 2 - endo - methylenedicarboxylic anhydride (1.07 g, 5.91 mmol), 1 - (3 - aminopropyl) - 4 - (2 - chlorophenyl)piperazine (1.5 g, 5.91 mmol) and n-butanol (15 ml) was refluxed for 6.5 hours. Then, the mixture was post-treated in the similar manner as that in Example 14 except that 5% hydrogen chloride was used in place of 15% hydrogen chloride to give N - [3 - {4 - (2 - chlorophenyl) - 1 - piperazinyl}propyl]bicyclo[2.2.1]heptane - 2 - exo - 2 - endo - methylene-dicarboximide hydrochloride (from isopropanol) (1.39 g, 51.5%). M.P., 220—221°C.

Example 19

A mixture of bicyclo[2.2.1]oct - 5 - ene - 2 - exo - 2 - endo - methylenedicarboxylic anhydride (1.6 g, 8.07 mmol), 1 - (4 - aminobutyl) - 4 - (2 - pyrimidinyl)piperazine (1.9 g, 8.07 mmol) and n-butanol (19 ml) was refluxed for 6 hours. The solvent was removed from the mixture under reduced pressure and the residue was purified by silica gel chromatography using chloroform as an eluent to give an oily substance (2.8 g, 84.9%). The oily substance (500 mg) was treated with 5% hydrogen chloride/isopropanol and recrystallized from isopropanol to give N - [4 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}butyl]bicyclo[2.2.1]-oct - 5 - ene - 2 - exo - 2 - endo - methylenedicarboximide hydrochloride (340 mg). M.P., 202—206°C.

Example 20

A mixture of N - [4 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}butyl]bicyclo[2.2.2]oct - 5 - ene - 2 - exo - 2 - endo - methylenedicarboximide (2.3 g, 5.62 mmol), 5% palladium on carbon (690 mg) and tetrahydrofuran (23 ml) was hydrogenated at an internal temperature of 50—60°C for 5 5/6 hours. Floating matter was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was treated with 5% hydrogen chloride/isopropanol and recrystallized from isopropanol to give N - [4 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}butyl]bicyclo[2.2.2]octane - 2 - exo - 2 - endo - methylene-dicarboximide hydrochl ride (780 mg, 28.7%). M.P., 245—247°C.

Example 21

A mixture of bicyclo[2.2.2] ctane - 2 - exo - 2 - endo - methylen dicarboxylic anhydride (725 mg,

3.73 mmol), 1 - (4 - aminobutyl) - 4 - (2 - chl rophenyl)pip razin (1 g, 3.73 mm l) and n-butan l (10 ml) was refluxed for 1.5 hours. The solv nt was rem v d from the mixture under r duced pressure and the residue was purified by silica gel chromatography using chlorof rm as an luent. Th ily substance btained was treated with 5% hydrogen chloride/isopropanol and recrystallized from is propan l/ether to give N - [4 - {4 - (2 - chl rophenyl) - 1 - pip razinyl}butyl]bicycl [2.2.2]octane - 2 - x - 2 - endo - methylenedicarboximide hydrochloride (970 mg, 50.3%). M.P., 203—204°C.

Example 22

A mixture of bicyclo[2.2.2]octane - 2 - exo - 2 - endo - methylenedicarboxylic anhydride (600 mg, 3.09 mmol), 1 - (3 - aminopropyl) - 4 - (2 - pyrimidinyl)piperazine (684 mg, 3.09 mmol) and n-butanol (6.8 ml) was refluxed for 5 hours. Then, the mixture was treated in a similar manner to that in Example 21 to give N - [3 - {4 - (2 - pyrimidinyl) - 1 - piperazinyl}propyl]bicyclo[2.2.2]octane - 2 - exo - 2 - endo - methylenedicarboximide hydrochloride (from isopropanol (1.0 g, 66.2%). M.P., 201—203°C

Example 23

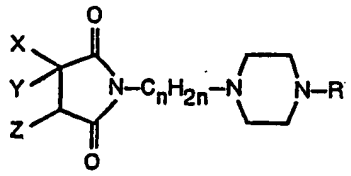
A mixture of bicyclo[2.2.2]octane - 2 - exo - 2 - endo - methylenedicarboxylic anhydride (600 mg, 3.09 mmol), 1 - (3 - aminopropyl) - 4 - (2 - pyridyl)piperazine (681 mg, 3.09 mmol) and n-butanol (6.8 ml) was refluxed for 5 hours. Then, the mixture was treated in a similar manner to that in Example 21 to giv N - [3 - {4 - (2 - pyridyl) - 1 - piperazinyl}propyl]bicyclo[2.2.2]octane - 2 - exo - 2 - endo - methylene-dicarboximide hydrochloride (from isopropanol) (940 mg, 64.8%). M.P., 214—215°C.

Example 24

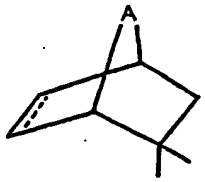
A mixture of bicyclo[2.2.2]octane - 2 - exo - 2 - endo - methylenedicarboxylic anhydride (600 mg, 3.09 mmol), 1 - (3 - aminopropyl) - 4 - phenylpiperazine (678 mg, 3.09 mmol) and n-butanol (6.8 ml) was refluxed for 3 1/6 hours. Then, the mixture was treated in a similar manner to that in Example 21 to give N - [3 - (4 - phenylpiperazinyl)propyl]bicyclo[2.2.2]octane - 2 - exo - 2 - endo - methylenedicarboximide hydrochloride (from methanol/ethanol) (880 mg, 60.7%). M.P., 233—235°C.

Claims for the Contracting States: BE CH DE FR GB IT LI NL SE

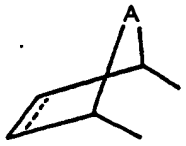
1. A succinimide derivative of the formula:



wherein X and Y are combined to form a group of the formula:

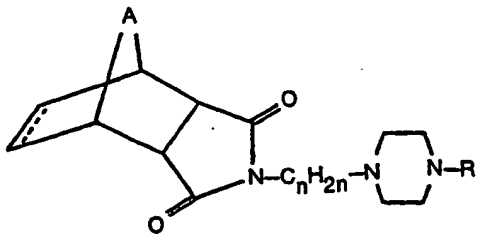


(wherein A is an oxygen atom, a methylene group or an ethylene group and a full line accompanying a broken line (----) is a single bond or a double bond) and Z is a hydrogen atom or, X and Z are combined to form a group of the formula:



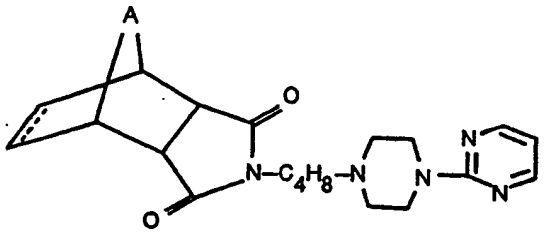
(wherein A and the full line accompanying a broken line are ach as defined above) and Y is a hydr gen atom, R is a phenyl group, optionally substituted with halogen, C_1—C_4 alkyl, C_1—C_4 alkoxy or trifluorom thyl, a 2-pyridyl group or a 2-pyrimidinyl group and n is an integer of 3 or 4, or pharmaceutically acceptabl acid additi n salt thereof.

2. The succinimide derivative as claimed in claim 1, which is a compound f the formula:



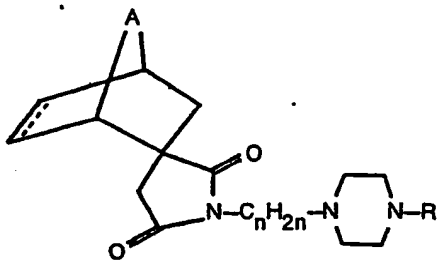
wherein A, the full line accompanying a broken line, R and n are each as defined in claim 1.

3. The succinimide derivative as claimed in claim 2, which is a compound of the formula:



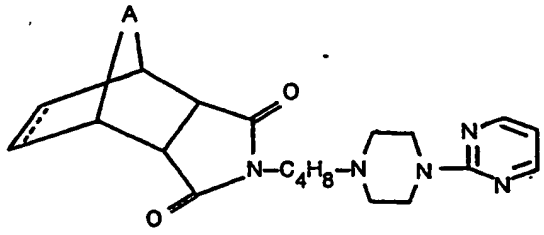
wherein A^1 is a methylene group or an ethylene group and the full line accompanying a broken line is as defined in claim 2.

4. The succinimide derivative as claimed in claim 1, which is a compound of the formula:



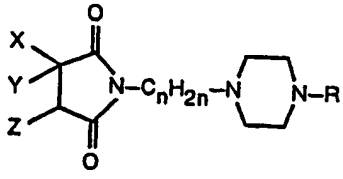
wherein A, the full line accompanying a broken line, R and n are each as defined in claim 1.

5. The succinimide derivative as claimed in claim 4, which is a compound of the formula:

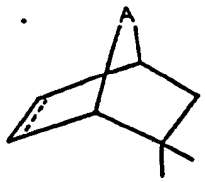


wherein A^1 is a methylene group or an ethylene group and the full line accompanying a broken line is as defined in claim 4.

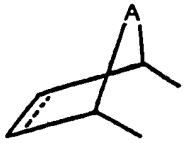
6. Process for preparing a succinimide derivative of the formula according to claim 1:



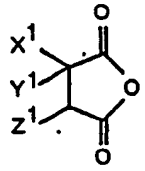
wherein X and Y are combined to form a group of the f rmula:



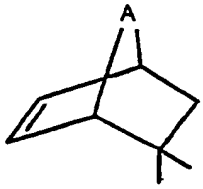
(wherein A is an oxygen atom, a methylene group or an ethylene group and a full line accompanying a broken line (------) is a single bond or a double bond) and Z is a hydrogen atom or, X and Z are combined to form a group of the formula:



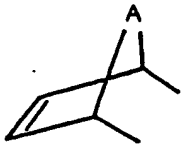
(wherein A and the full line accompanying a broken line are each as defined above) and Y is a hydrogen atom, R is a phenyl group, optionally substituted with halogen, C_1—C_4 alkyl, C_1—C_4 alkoxy or trifluoromethyl, a 2-pyridyl group or a 2-pyrimidinyl group and n is an integer of 3 or 4, which compris s reacting a compound of the formula:



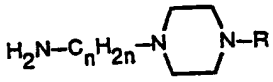
wherein X^1 and Y^1 are combined to form a group of the formula:



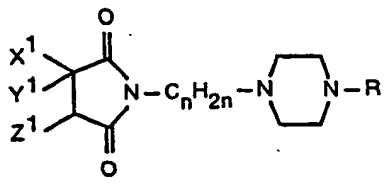
(wherein A is as defined above) and Z^1 is a hydrogen atom or, X^1 and Z^1 are combined to form a group of the formula:



(wherein A is as defined above) and Y^1 is a hydrogen atom, and R and n are each as defined, with an amine of the formula:

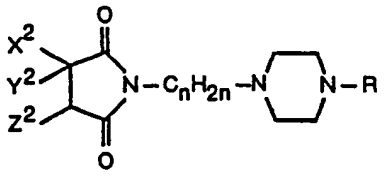


wherein R and n are each as defined above, and optionally reducing a resulting compound of the formula:

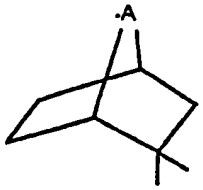


wherein X^1 and Y^1, Z^1, R and n are each as defined above.

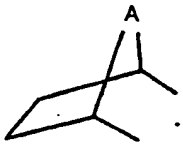
7. A process for preparing a compound of the formula according to claim 1:



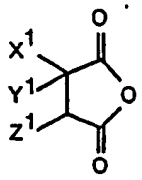
wherein X^2 and Y^2 are combined to form a group of the formula:



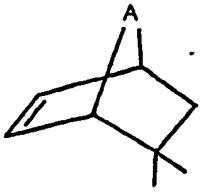
(wherein A is an oxygen atom, a methylene group or an ethylene group) and Z^2 is a hydrogen atom or, X^2 and Z^2 are combined to form a group of the formula:



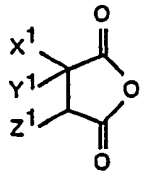
(wherein A is as defined above) and Y^2 is a hydrogen atom, R is a phenyl group, optionally substituted with halogen, C_1—C_4 alkyl, C_1—C_4 alkoxy or trifluoromethyl, a 2-pyridyl group or a 2-pyrimidinyl group and n is an integer of 3 or 4, which comprises reducing a compound of the formula:



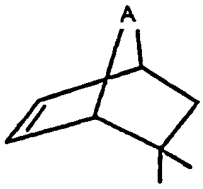
wherein X^1 and Y^1 are combined to form a group of the formula:



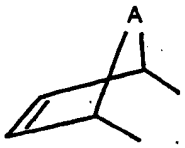
(wherein A is as defined above) and Z^1 is a hydrogen atom, or X^1 and Z^1 are combined to form a group of the formula:



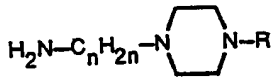
wherein X^1 and Y^1 are combined to form a group of the formula:



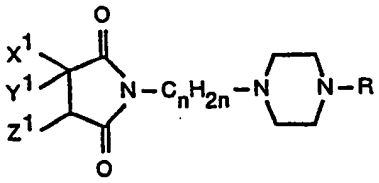
(wherein A is as defined above) and Z^1 is a hydrogen atom or, X^1 and Z^1 are combined to form a group of the formula:



(wherein A is as defined above) and Y^1 is a hydrogen atom, and R and n are each as defined, with an amine of the formula:

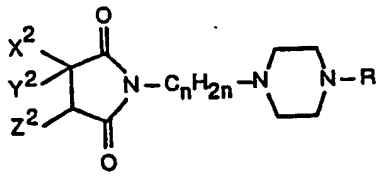


wherein R and n are each as defined above, optionally reducing a resulting compound of the formula:

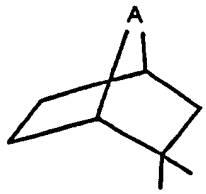


wherein X^1 and Y^1, Z^1, R and n are each as defined above and optionally converting the compound obtained in its pharmaceutically acceptable acid addition salt.

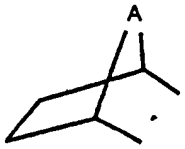
2. A process for preparing a compound of the formula



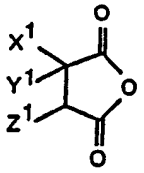
wherein X^2 and Y^2 are combined to form a group of the formula:



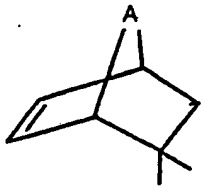
(wherein A is an oxygen atom, a methylene group or an ethylene group) and Z^2 is a hydrogen atom or, X^2 and Z^2 are combined to form a group of the formula:



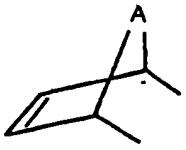
(wherein A is as defined above) and Y^2 is a hydrogen atom, R is a phenyl group, optionally substituted with halogen, C_1—C_4 alkyl, C_1—C_4 alkoxy or trifluoromethyl, a 2-pyridyl group or a 2-pyrimidinyl group and n is an integer of 3 or 4, which comprises reducing a compound of the formula:



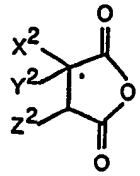
wherein X^1 and Y^1 are combined to form a group of the formula:



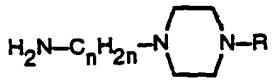
(wherein A is as defined above) and Z^1 is a hydrogen atom, or X^1 and Z^1 are combined to form a group of the formula:



(wherein A is as defined above) and Y^1 is a hydrogen atom, and R and n are each as defined above, reacting the resulting compound of the formula:

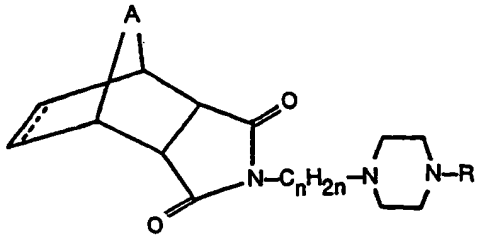


wherein X^2, Y^2 and Z^2 are each as defined above, with an amine of the formula:



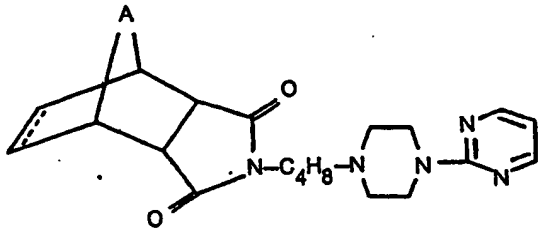
wherein R and n are each as defined above and optionally converting the compound obtained in its pharmaceutically acceptable acid addition salt.

3. A process as claimed in claim 1 or 2 for preparing a succinimide derivative of the formula:



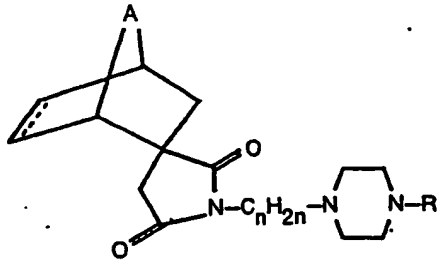
wherein A, the full line accompanying a broken line, R and n are each as defined in claim 1.

4. A process as claimed in claim 1 or 2 for preparing a succinimide derivative of the formula:



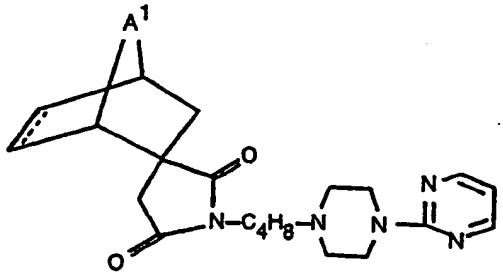
wherein A^1 is a methylene group or an ethylene group and the full line accompanying a broken line is as defined in claim 1.

5. A process as claimed in claim 1 or 2 for preparing a succinimide derivative of the formula:



wherein A, the full line accompanying a broken line, R and n are each as defined in claim 1.

6. A process as claimed in claim 1 or 2 for preparing a succinimide derivative of the formula:

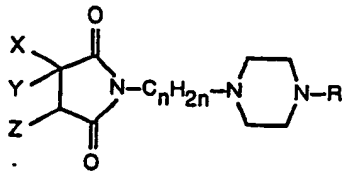


wherein A^1 is a methylene group or an ethylene group and the full line accompanying a broken line is as defined in claim 1.

7. A process for preparing a pharmaceutical composition which comprises the formulation of a pharmaceutically effective amount of at least one of the compounds defined in claim 1 as an active ingredient and at least one pharmaceutically acceptable inert carrier or diluent.

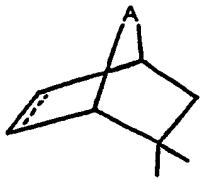
Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI NL SE

1. Succinimid-Derivat der Formel:

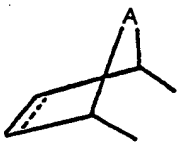


(I)

worin X und Y unter Bildung einer Gruppe der Formel:

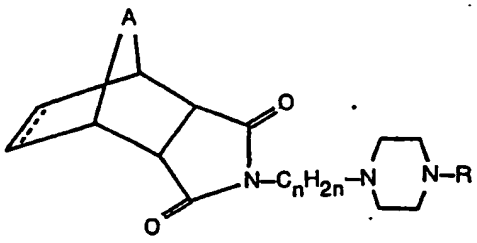


[worin A ein Sauerstoffatom, eine Methylengruppe oder eine Ethylengruppe ist und eine ausgezogene Linie, die eine unterbrochene Linie begleitet (----), eine Einfachbindung oder eine Doppelbindung ist] kombiniert sind und Z ein Wasserstoffatom ist oder X und Z unter Bildung einer Gruppe der Formel:



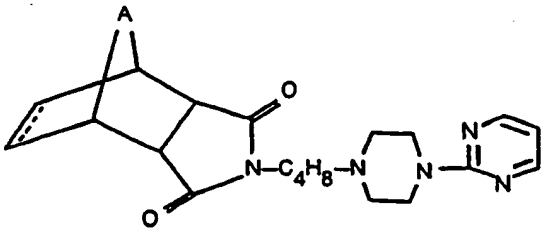
(worin A und die ausgezogene Linie, die eine unterbrochene Linie begleitet, jeweils wie oben definiert sind) kombiniert sind und Y eine Wasserstoffatom ist, R eine Phenylgruppe, die gegebenenfalls durch Halogen, Alkyl mit 1 bis 4 Kohlenstoffatomen, Alkoxy mit 1 bis 4 Kohlenstoffatomen oder Trifluormethyl substituiert ist, eine 2-Pyridylgruppe oder eine 2-Pyrimidinylgruppe ist und n eine ganze Zahl von 3 oder 4 ist, oder pharmazeutisch unbedenkliche Säureadditionssalaze davon.

2. Succinimid-Derivat, wie in Anspruch 1 beansprucht, das eine Verbindung der Formel:



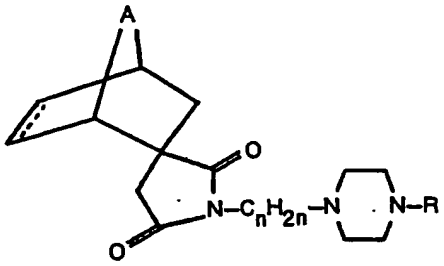
ist, worin A, die ausgezogene Linie, die eine unterbrochene Linie begleitet, R und n jeweils wie in Anspruch 1 definiert sind.

3. Succinimid-Derivat, wie in Anspruch 2 beansprucht, das eine Verbindung der Formel:



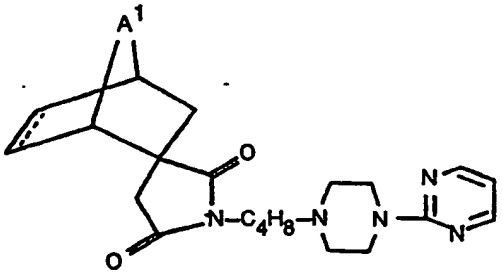
ist, worin A^1 eine Methylengruppe oder eine Ethylengruppe ist und die ausgezogene Linie, die eine unterbrochene Linie begleitet, wie in Anspruch 2 definiert ist.

4. Succinimid-Derivat, wie in Anspruch 1 beansprucht, das eine Verbindung der Formel:



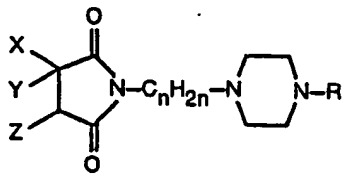
ist, worin A, die ausgezogene Linie, die eine unterbrochene Linie begleitet, R und n jeweils wie in Anspruch 1 definiert sind.

5. Succinimid-Derivat, wie in Anspruch 4 beansprucht, das eine Verbindung der Formel:

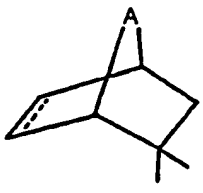


ist, worin A^1 eine Methylengruppe oder eine Ethylengruppe ist und die ausgezogene Linie, die eine unterbrochene Linie begleitet, wie in Anspruch 4 definiert ist.

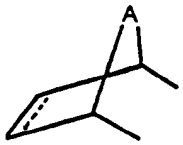
6. Verfahren zur Herstellung eines Succinimid-Derivates der Formel gemäss Anspruch 1:



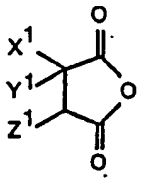
worin X und Y unter Bildung einer Gruppe der Formel:



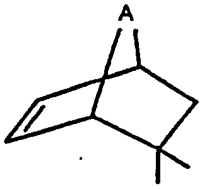
[worin A ein Sauerstoffatom, eine Methylengruppe od r eine Ethylengruppe ist und eine ausgez gene Linie, die eine unterbrochene Linie begleitet (----), eine Einfachbindung oder ine Doppelbindung ist] kombiniert sind und Z ine Wasserstoffatom ist der X und Z unter Bildung einer Gruppe der Formel:



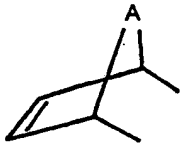
(worin A und die ausgezogene Linie, die eine unterbrochene Linie begleitet, jeweils wie oben definiert sind) kombiniert sind und Y ein Wasserstoffatom ist, R eine Phenylgruppe, die gegebenenfalls durch Halogen, Alkyl mit 1 bis 4 Kohlenstoffatomen, Alkoxy mit 1 bis 4 Kohlenstoffatomen oder Trifluormethyl substituiert ist, eine 2-Pyridylgruppe oder eine 2-Pyrimidinylgruppe ist und n eine ganze Zahl von 3 oder 4 ist, dadurch gekennzeichnet, dass man eine Verbindung der Formel:



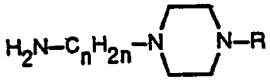
worin X^1 und Y^1 unter Bildung einer Gruppe der Formel:



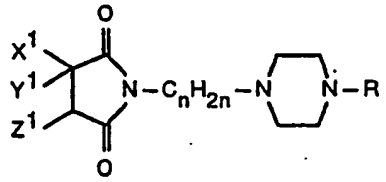
(worin A wie oben definiert ist) kombiniert sind und Z^1 eine Wasserstoffatom ist oder X^1 und Z^1 unter Bildung einer Gruppe der Formel:



(worin A wie oben definiert ist) kombiniert sind und Y^1 ein Wasserstoffatom ist und R und n jeweils wie oben definiert sind, mit einem Amin der Formel:

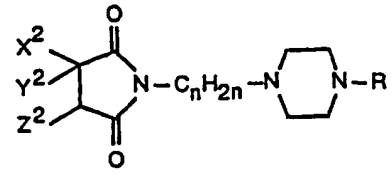


worin R und n jeweils wie oben definiert sind, umsetzt und gegebenenfalls eine resultierende Verbindung der Formel:

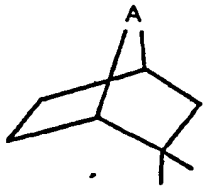


worin X^1 und Y^1, Z^1, R und n jeweils wie oben definiert sind, r duziert.

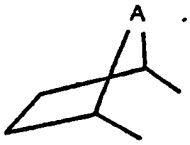
7. Verfahren zur Herstellung einer Verbindung der F rm l g mäss Anspruch 1:



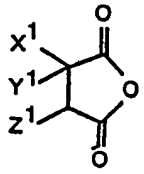
worin X^2 und Y^2 unter Bildung einer Gruppe der Formel:



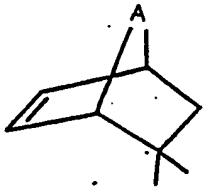
(worin A ein Sauerstoffatom, eine Methylengruppe oder eine Ethylengruppe ist) kombiniert sind und Z^2 ein Wasserstoffatom ist oder X^2 und Z^2 unter Bildung einer Gruppe der Formel:



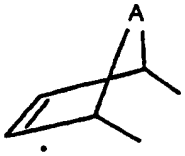
(worin A wie oben definiert ist) kombiniert sind und Y^2 ein Wasserstoffatom ist, R eine Phenylgruppe, die gegebenenfalls durch Halogen, Alkyl mit 1 bis 4 Kohlenstoffatomen, Alkoxy mit 1 bis 4 Kohlenstoffatomen oder Trifluormethyl substituiert ist, eine 2-Pyridylgruppe oder 2-Pyrimidinylgruppe bedeutet und n eine ganze Zahl von 3 oder 4 ist, dadurch gekennzeichnet, dass man eine Verbindung der Formel:



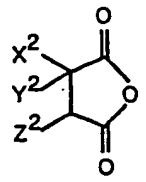
worin X^1 und Y^1 unter Bildung einer Gruppe der Formel:



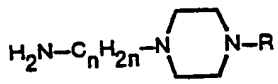
(worin A wie oben definiert ist) kombiniert sind und Z^1 ein Wasserstoffatom ist oder X^1 und Z^1 unter Bildung einer Gruppe der Formel:



(worin A wie oben definiert ist) kombiniert sind und Y^1 ein Wasserstoffatom ist und R und n jeweils wie oben definiert sind, reduziert, die resultierende Verbindung der Formel:



worin X^2, Y^2 und Z^2 jeweils wie oben definiert sind, mit einem Amin der Formel:

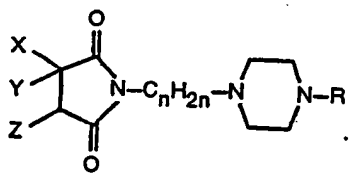


worin R und n jeweils wie oben definiert sind, umsetzt.

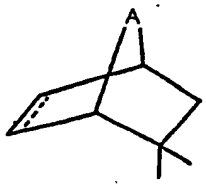
8. Pharmazeutisches Mittel, das als Wirkstoffkomponente eine pharmazeutisch wirksame Menge mindestens eine der in Anspruch 1 beanspruchten Verbindungen sowie mindestens einen pharmazeutisch unbedenklichen inerten Träger oder mindestens ein pharmazeutisch unbedenkliches inertes Verdünnungsmittel enthält.

Patentansprüche für den Vertragsstaat: AT

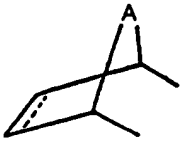
1. Verfahren zur Herstellung eines Succinimid-Derivates der Formel:



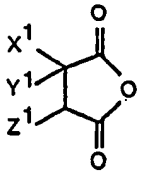
worin X und Y unter Bildung einer Gruppe der Formel:



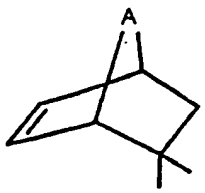
[worin A eine Sauerstoffatom, eine Methylengruppe oder eine Ethylengruppe ist und eine ausgezog ne Linie, die eine unterbrochene Linie begleitet (- - - -), eine Einfachbindung oder eine Doppelbindung ist] kombiniert sind und Z eine Wasserstoffatom ist oder X und Z unter Bildung einer Gruppe der Formel:



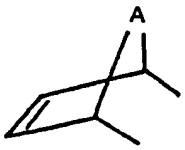
(worin A und die ausgezogene Linie, die eine unterbrochene Linie begleitet, jeweils wie oben definiert sind) kombiniert sind und Y eine Wasserstoffatom ist, R eine Phenylgruppe, die gegebenenfalls durch Halog n, Alkyl mit 1 bis 4 Kohlenstoffatomen, Alkoxy mit 1 bis 4 Kohlenstoffatomen oder Trifluormethyl substitui rt ist, eine 2-Pyridylgruppe oder eine 2-Pyrimidinylgruppe ist und n eine ganze Zahl von 3 oder 4 ist, dadurch gekennzeichnet, dass man eine Verbindung der Formel:



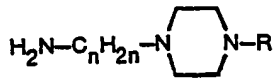
worin X^1 und Y^1 unter Bildung einer Gruppe der Formel:



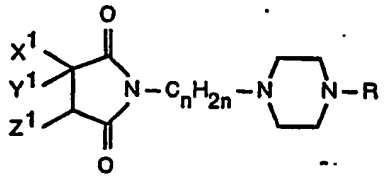
(worin A wie oben definiert ist) kombiniert sind und Z^1 ein Wasserstoffatom ist oder X^1 und Z^1 unter Bildung einer Gruppe der Formel:



(worin A wie oben definiert ist) kombiniert sind und Y^1 ein Wasserstoffatom ist und R und un jeweils wie oben definiert sind, mit einem Amin der Formel:

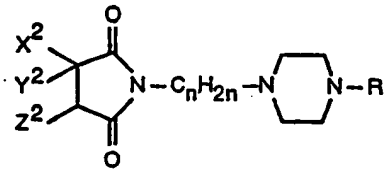


worin R und n jeweils wie oben definiert sind, umsetzt, gegebenenfalls eine resultierende Verbindung der Formel:

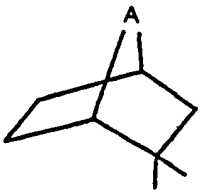


worin X^1 und Y^1, Z^1, R und n jeweils wie oben derfiniert sind, reduziert und gegebenenfalls die erhaltene Verbindung in ihr pharmazeutisch unbedenkliches Säureadditionssalz überführt.

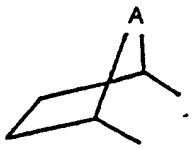
2. Verfahren zur Herstellung einer Verbindung der Formel:



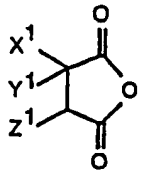
worin X^2 und Y^2 unter Bildung einer Gruppe der Formel:



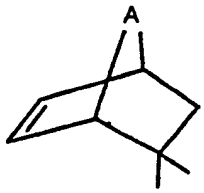
(worin A ein Sauerstoffatom, eine Methylengruppe oder eine Ethylengruppe ist) kombiniert sind und Z^2 ein Wasserstoffatom ist oder X^2 und Z^2 unter Bildung einer Gruppe der Formel:



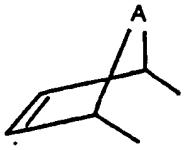
(worin A wie oben definiert ist) kombiniert sind und Y^2 ein Wasserstoffatom ist, R eine Phenylgruppe, die gegebenenfalls durch Halogen, Alkyl mit 1 bis 4 Kohlenstoffatomen, Alkoxy mit 1 bis 4 Kohlenstoffatomen oder Trifluormethyl substituiert ist, eine 2-Pyridylgruppe oder 2-Pyrimidinylgruppe ist und n eine ganze Zahl von 3 oder 4 ist, dadurch gekennzeichnet, dass man eine Verbindung der Formel:



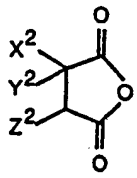
worin X^1 und Y^1 unter Bildung einer Gruppe der Formel:



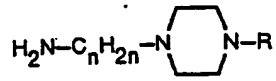
(worin A wie oben definiert ist) kombiniert sind und Z^1 ein Wasserstoffatom ist oder X^1 und Z^1 unter Bildung einer Gruppe der Formel:



(worin A wie oben definiert ist) kombiniert sind und Y^1 ein Wasserstoffatom ist und R und n jeweils wi oben definiert sind, reduziert, die resultierende Verbindung der Formel:

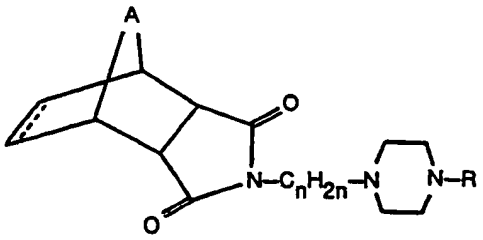


worin X^2, Y^2 und Z^2 jeweils wie oben definiert sind, mit einem Amin der Formel:



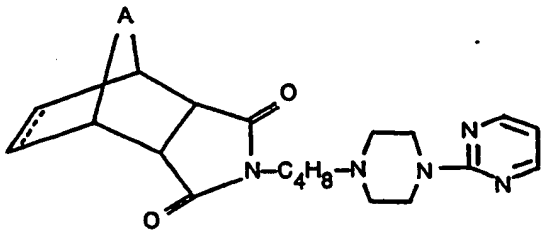
worin R und n jeweils wie oben definiert sind, umsetzt und gegebenenfalls die erhaltene Verbindung in ihr pharmazeutisch unbedenkliches Säureadditionssalz überführt.

3. Verfahren, wi in Anspruch 1 oder 2 beansprucht, zur Herstellung ein s Succinimid-Derivat s der Form I:



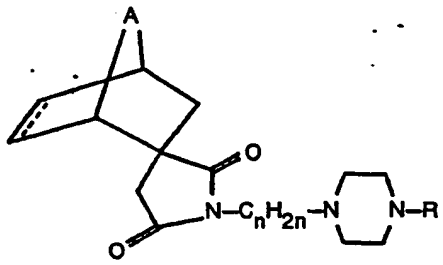
worin A, die ausgezogene Linie, die eine unterbrochene Linie begleitet, R und n jeweils wie in Anspruch 1 definiert sind.

4. Verfahren, wie in Anspruch 1 oder 2 beansprucht, zur Herstellung eines Succinimid-Derivates der Formel:



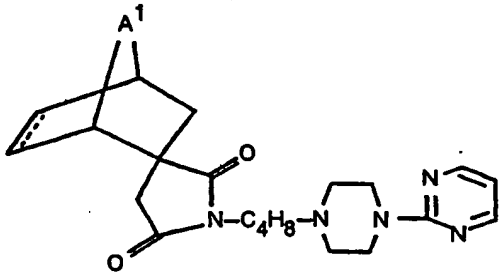
worin A^1 eine Methylengruppe oder eine Ethylengruppe ist und die ausgezogene Linie, die eine unterbrochene Linie begleitet, wie in Anspruch 1 definiert ist.

5. Verfahren, wie in Anspruch 1 oder 2 beansprucht, zur Herstellung eines Succinimid-Derivates der Formel:



worin A, die ausgezogene Linie, die eine unterbrochene Linie begleitet, R und n jeweils wie in Anspurch 1 definiert sind.

6. Verfahren, wie in Anspruch 1 oder 2 beansprucht, zur Herstellung eines Succinimid-Derivates der Formel:

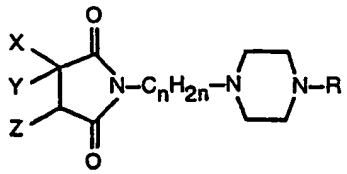


worin A^1 eine Methylengruppe oder eine Ethylengruppe ist und die ausgezogene Linie, die eine unterbrochene Linie begleitet, wie in Anspruch 1 definiert ist.

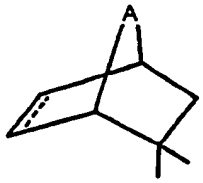
7. Verfahren zur Herstellung eines pharmazeutisch n Mittels, gekennzeichnet durch die Formulierung einer pharmazeutisch wirksam n Menge mindestens einer der in Anspruch 1 definiert n Verbindungen als Wirkstoffkompon nt und mindestens eines pharmazeutisch unbedenklichen inerten Trägers oder Verdünnungsmitt ls.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI NL SE

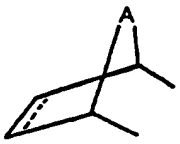
1. Dérivé de succinimide de la formule:



dans laquelle X et Y sont combinés pour former un radical de la formule:

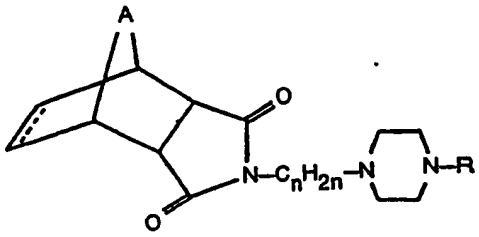


(dans laquelle A représente un atome d'oxygène, un radical méthylène ou un radical éthylène et une ligne en trait plein accompagnant une ligne en traits interrompus (- - - -) représente une simple liaison ou une double liaison) et Z représente un atome d'hydrogène, ou bien X et Z sont combinés pour former un radical de la formule:



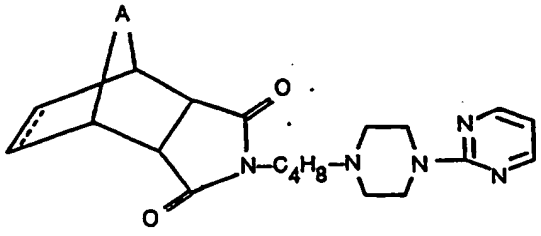
(dans laquelle A et une ligne en trait plein accompagnant une ligne en traits interrompus possèdent chacun les significations qui leur ont été précédemment attribuées) et Y représente un atome d'hydrogène, R représente un radical phényle éventuellement substitué par des atomes d'halogènes, des radicaux alkyl en C_1—C_4, alcoxy en C_1—C_4 ou trifluorométhyle, un radical 2-pyridyle ou un radical 2-pyrimidinyle et n représente un nombre entier égal à 3 ou à 4, ou un sel d'addition d'acide pharmaceutiquement acceptable d'un tel dérivé.

2. Dérivé de succinimide suivant la revendication 1, caractérisé en ce qu'il est un composé de la formule:



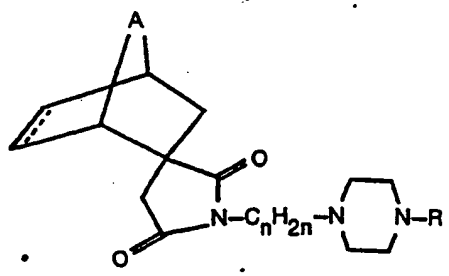
dans laquelle A, la ligne en trait plein accompagnant une ligne en traits interrompus, R et n possèdent chacun les significations qui leur ont été attribuées dans la revendication 1.

3. Dérivé de succinimide suivant la revendication 2, caractérisé en ce que c'est un composé de la formule:



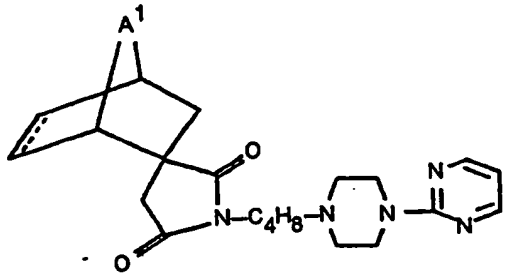
dans laquelle A^1 représente un groupe méthylène ou un groupe éthylène et la ligne en trait plein accompagnant une ligne en traits interrompus possède les significations qui lui ont été attribuées dans la revendication 2.

4. Dérivé de succinimide suivant la revendication 1, caractérisé en ce qu'il est un composé de la formule:



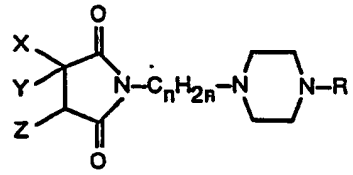
dans laquelle A, la ligne en trait plein accompagnant une ligne en traits interrompus, R et n possèdent chacun les significations qui leur ont été attribuées dans la revendication 1.

5. Dérivé de succinimide suivant la revendication 4, caractérisé en ce que c'est un composé de la formule:

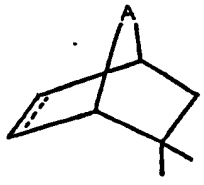


dans laquelle A^1 représente un groupe méthylène ou un groupe éthylène et la ligne en trait plein accompagnant une ligne en traits interrompus possède les significations qui lui ont été attribuées dans la revendication 4.

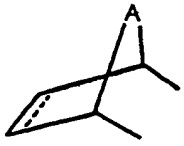
6. Procédé pour préparer un dérivé du succinimide de la formule suivant la revendication 1:



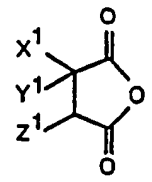
dans laquelle X et Y sont combinés pour former un radical de la formule:



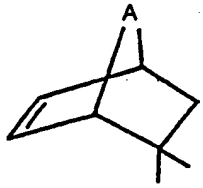
(dans laquelle A représente un atome d'oxygène, un radical méthylène ou un radical éthylène et une ligne en trait plein accompagnant une ligne en traits interrompus (----) représente une simple liaison ou une double liaison) et Z représente un atome d'hydrogène, ou bien X et Z sont combinés pour former un radical de la formule:



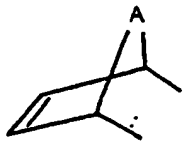
(dans laquelle A et une ligne en trait plein accompagnant une ligne en traits interrompus possèdent chacun les significations qui leur ont été précédemment attribuées) et Y représente un atome d'hydrogèn , R représ nte un radical phényle éventuellement substitué par d s atomes d'halogènes, des radicaux alkyle en C_1—C_4, alcoxy n C_1—C_4 ou trifluorométhyl , un radical 2-pyridyl ou un radical 2-pyrimidinyle et n représ nte un nombre ntier égal à 3 ou à 4, caractérisé en ce que l' n fait réagir un comp sé d la formule:



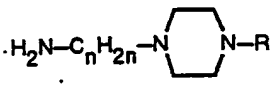
dans laquelle X^1 et Y^1 sont combinés pour former un composé de la formule:



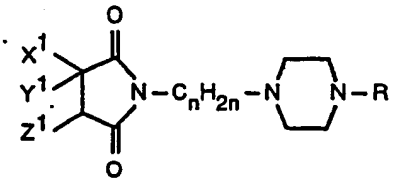
(dans laquelle A possède les significations qui lui ont été précédemment attribuées) et Z^1 représente un atome d'hydrogène, ou bien X^1 et Z^1 sont combinés pour former un groupe de la formule:



(dans laquelle A possède les significations qui lui ont été précédemment attribuées) et Y^1 représente un atome d'hydrogène et R et n possèdent chacun les significations qui leur ont été précédemment attribuées, sur une amine de la formule: .

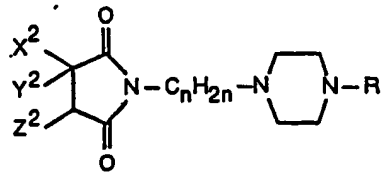


dans laquelle R et n possèdent chacun les significations qui leur ont été précédemment attribuées et n réduit éventuellement un composé obtenu de la formule:

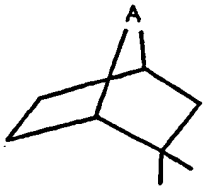


dans laquelle X^1 et Y^1, Z^1, R et n possèdent chacun les significations qui leur ont été précédemment attribuées.

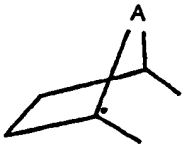
7. Procédé de préparation d'un composé de la formule suivant la revendication 1:



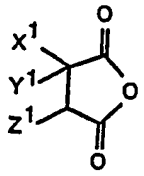
dans laquelle X^2 et Y^2 sont combinés pour former un groupe de la f rmule:



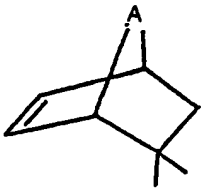
(dans laquelle A représente un atome d'oxygène, un radical méthylène ou un radical éthylène) et Z^2 représente un atome d'hydrogène, ou bien X^2 et Z^2 sont combinés pour former un groupe de la formule:



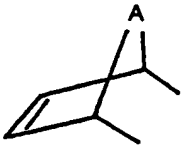
(dans laquelle A possède les significations qui lui ont été précédemment attribuées) et Y^2 représente un atome d'hydrogène, R représente un radical phényle, éventuellement substitué par des halogènes, des radicaux alkyle en C_1—C_4, alcoxy en C_1—C_4 ou trifluorométhyle, un radical 2-pyridyle ou un radical 2-pyrimidinyle et n représente un nombre entier égal à 3 ou à 4, caractérisé en ce que l'on réduit un composé de la formule:



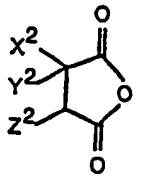
dans laquelle X^1 et Y^1 sont combinés pour former un groupe de la formule:



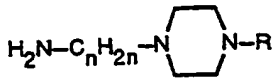
(dans laquelle A possède les significations qui lui ont été précédemment attribuées) et Z représente un atome d'hydrogène, ou bien X^1 et Z^1 sont combinés pour former un groupe de la formule:



(dans laquelle A possède les significations qui lui ont été précédemment attribuées) et Y^1 représente un atome d'hydrogène et R et n possèdent chacun les significations qui leur ont été précédemment attribuées, on fait réagir le composé résultant de la formule:



dans laquelle X^2, Y^2 et Z^2 possèdent chacun les significations qui leur ont été précédemment attribuées, sur une amine de la formule:

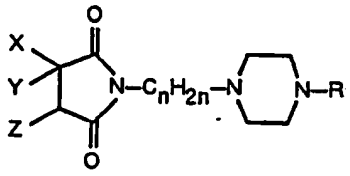


dans laquelle R et n possèdent chacun les significations qui leur ont été précédemment attribuées.

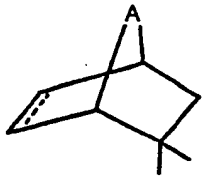
8. Composition pharmaceutique, caractérisée en ce qu'elle contient, à titre d'ingrédient actif, un quantité pharmaceutiquement efficace d'au moins un des composés suivant la revendication 1 et au moins un diluant, véhicule ou excipient inerte pharmaceutiquement acceptable.

Revendications pour l'Etant contractant: AT

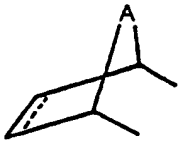
1. Procédé de préparation d'un dérive de succinimide de la formule:



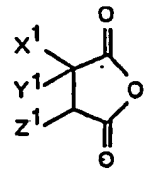
dans laquelle X et Y sont combinés pour former un radical de la formule:



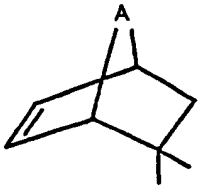
(dans laquelle A représente un atome d'oxygène, un radical méthylène ou un radical éthylène et une ligne en trait plein accompagnant une ligne en traits interrompus (----) représente une simple liaison ou une double liaison) et Z représente un atome d'hydrogène, ou bien X et Z sont combinés pour former un radical de la formule:



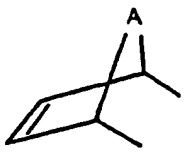
(dans laquelle A et une ligne en trait plein accompagnant une ligne en traits interrompus possèdent chacun les significations qui leur ont été précédemment attribuées) et Y représente un atome d'hydrogène, R représente un radical phényle éventuellement substitué par des atomes d'halogènes, des radicaux alkyle en C_1—C_4, alcoxy en C_1—C_4 ou trifluorométhyle, un radical 2-pyridyle ou un radical 2-pyrimidinyle n n représente un nombre entier égal à 3 ou à 4, caractérisé en ce que l'on fait réagir un composé de la formule:



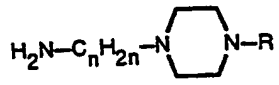
dans laquelle X^1 et Y^1 sont combinés pour former un composé de la formule:



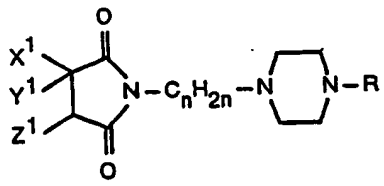
(dans laquelle A possède les significations qui lui ont été précédemment attribuées) et Z^1 représent un atome d'hydrogène, ou bien X^1 et Z^1 sont combinés pour former un groupe de la formule :



(dans laquelle A possède les significations qui lui ont été précédemment attribuées) et Y^1 représente un atome d'hydrogène et R et n possèdent chacun les significations qui leur ont été précédemment attribuées, sur une amine de la formule:

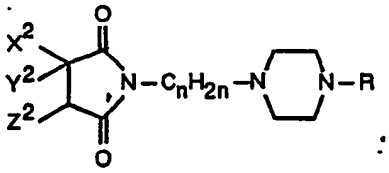


dans laquelle R et n possèdent chacun les significations qui leur ont été précédemment attribuées et on réduit éventuellement un composé de la formule:

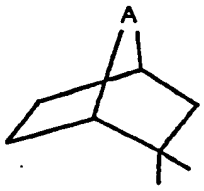


dans laquelle X^1 et Y^1, Z^1, R et n possèdent chacun les significations qui leur ont été précédemment attribuées et on convertit éventuellement le composé obtenu en son sel d'addition d'acide pharmaceutiquement acceptable.

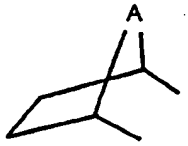
2. Procédé de préparation d'un composé de la formule:



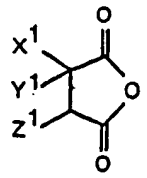
dans laquelle X^2 et Y^2 sont combinés pour former un groupe de la formule:



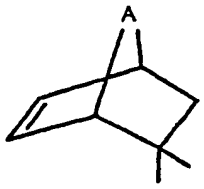
(dans laquelle A représente un atome d'oxygène, un radical méthylène ou un radical éthylène) et Z^2 représente un atome d'hydrogène, ou bien X^2 et Z^2 sont combinés pour former un groupe de la formule:



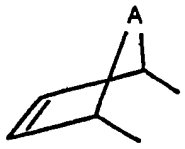
(dans laquelle A possède les significations qui lui ont été précédemment attribuées) et Y^2 représente un atome d'hydrogèn , R représente un radical phényle, éventuellement substitué par des halogènes, des radicaux alkyle en C_1—C_4, alcoxy en C_1—C_4 u.trifluorométhyle, un radical 2-pyridyle u un radical 2-pyrimidinyle et n représ nte un nombre entier égal à 3 ou à 4, caractérisé en ce que l'on réduit un composé de la formule:



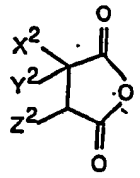
dans laquelle X^1 et Y^1 sont combinés pour former un groupe de la formule:



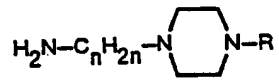
(dans laquelle A possède les significations qui lui ont été précédemment attribuées) et Z représente un atome d'hydrogène, ou bien X^1 et Z^1 sont combinés pour former un groupe de la formule:



(dans laquelle A possède les significations qui lui ont été précédemment attribuées) et Y^1 représente un atome d'hydrogène et R et n possèdent chacun les significations qui leur ont été précédemment attribuées, on fait réagir le composé résultant de la formule:

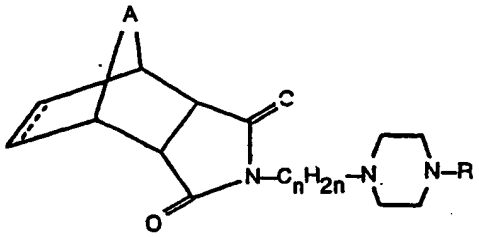


dans laquelle X^2, Y^2 et Z^2 possèdent chacun les significations qui leur ont été précédemment attribuées, sur une amine de la formule:



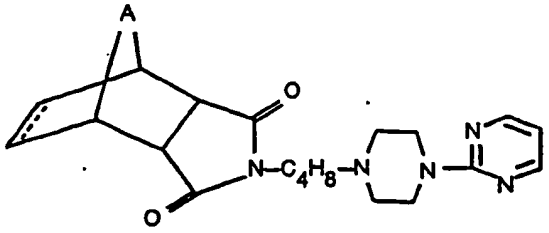
dans laquelle R et n possèdent chacun les significations qui leur ont été précédemment attribuées et on convertit éventuellement le composé obtenu en son sel d'addition pharmaceutiquement acceptable.

3. Procédé suivant l'une quelconque des revendications 1 et 2 de préparation d'un dérivé de succinimide de la formule:



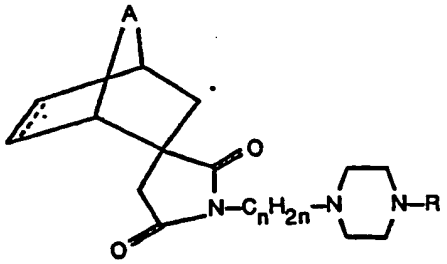
dans laquelle A, la ligne en trait plein accompagnant une ligne en traits interrompus, R et n possèdent chacun les significations qui leur ont été attribuées dans la revendication 1.

4. Procédé suivant l'une quelconque des revendications 1 et 2, de préparation d'un dérivé de succinimide de la formule:



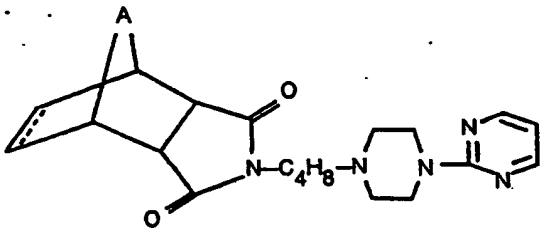
dans laquelle A^1 représente un radical méthylène ou un radical éthylène et la ligne en trait plein accompagnant une ligne en traits interrompus possède les significations qui lui ont été attribuées dans la revendication 1.

5. Procédé suivant l'une quelconque des revendications 1 et 2, de préparation d'un dérivé de succinimide de la formule:



dans laquelle A, la ligne en trait plein accompagnant une ligne en traits interrompus, R et n possèdent chacun les significations qui leur ont été attribuées dans la revendication 1.

6. Procédé suivant l'une quelconque des revendications 1 et 2, de préparation d'un dérivé de succinimide de la formule:



dans laquelle A^1 représente un radical méthylène ou un radical éthylène et la ligne en trait plein accompagnant une ligne en traits interrompus possède les significations qui lui ont été attribuées dans la revendication 1.

7. Procédé de préparation d'une composition pharmaceutique, caractérisé en ce qu'il comprend la mise en composition d'une quantité pharmaceutiquement efficace d'au moins un des composés définis dans la revendication 1 à titre d'ingrédient actif et d'au moins un diluant, véhicule ou excipient inerte pharmaceutiquement acceptable.